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Form Approved
OMB No. 0704-0188

(2)

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	1993	Reprint

4. TITLE AND SUBTITLE

(see title on reprint)

5. FUNDING NUMBERS

PE: NWED QAXM

WU: 00105

6. AUTHOR(S)

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

SR93-30

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

Uniformed Services University of the Health Sciences
4301 Jones Bridge Road
Bethesda, MD 20814-4799

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT

Approved for public release; distribution unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

14. SUBJECT TERMS

15. NUMBER OF PAGES

7

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
UNCLASSIFIED	UNCLASSIFIED		

CLASSIFIED BY:

DECLASSIFY ON:

RADIATION RESEARCH 136, 255–261 (1993)

Gamma Radiation (5–10 Gy) Impairs Neuronal Function in the Guinea Pig Hippocampus

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PELLMAR, T. C., AND LEPINSKI, D. L. Gamma Radiation (5–10 Gy) Impairs Neuronal Function in the Guinea Pig Hippocampus. *Radiat. Res.* 136, 255–261 (1993).

Guinea pigs were exposed to 5 and 10 Gy γ radiation. Hippocampal brain slices were isolated 30 min, 1 day, 3 days and 5 days after irradiation or sham irradiation and the electrophysiological characteristics of the neural tissue were evaluated. Both radiation doses elicited significant changes that were dependent on dose, dose rate and time. Synaptic efficacy decreased soon after exposure to 5 Gy at dose rates of both 1 and 20 Gy/min. Recovery occurred by 5 days. Ten grays at 20 Gy/min potentiated the postsynaptic potential 1 day after irradiation. By 3 days, synaptic efficacy was decreased and did not recover. The ability of the synaptic potentials to generate spikes was potentiated within 30 min after exposure to 5 Gy at 1 Gy/min and persisted through 3 days, with recovery at 5 days. At the 20 Gy/min dose rate, a similar potentiation did not result with 10 Gy and occurred only at 3 days after irradiation with 5 Gy. Rather, within 30 min and after 5 days, spike generation was significantly depressed by these exposures. Both synaptic efficacy and spike generation contribute to the net input–output relationship of the neuronal population. This relationship was profoundly decreased within 30 min with recovery at 1 day and subsequent decline with the higher dose rate in a dose-dependent manner. These persistent changes in neuronal function are likely to be a consequence of the actions of ionizing radiation on the physiological processes that influence the neuronal environment.

INTRODUCTION

Although the central nervous system is considered to be resistant to ionizing radiation, exposure to relatively low doses is known to alter behavior. Fatigue and weakness occur after exposure to doses of only 1 Gy in humans while disorientation is elicited by doses of 5 Gy (*1*). Studies in rats have shown that less than 5 Gy ionizing radiation can impair the learning of new tasks, the retention of learned tasks (*2*), and the transference of learning skills (*3*). These deficits are observed within a day of radiation exposure. In clinical studies, investigators have observed disruption of cognitive function in patients treated with radiotherapy (*4–6*). Neurophysiological changes occur concurrently with the behavioral effects. Within hours of irradiation with 10 Gy and less, altered neuronal firing patterns (*7*), modified synaptic potentials (*8*), and abnormal electroencephalographic activity (*9*) are evident.

Classically, neurons have been considered to be a primary radiation target only at high doses (>100 Gy) sufficient to cause the central nervous system syndrome (*10*). Some evidence for direct neuronal deficits at lower radiation doses comes from studies in our laboratory on guinea pig hippocampal brain slices irradiated *in vitro*. Neuronal electrophysiology was altered within hours by doses as low as 25 Gy (*11, 12*). At lower radiation doses, actions on glial cells and brain vasculature have been suggested as the primary sites of action. However, evidence of glial degeneration and vascular disruption appears only weeks to months after exposure (*13–15*) and therefore cannot explain the acute physiological and behavioral effects.

In an effort to understand the cellular basis for acute radiation effects at relatively low doses, the present study evaluates the neuronal deficits that result from exposure to *in vivo* whole-body irradiation. Under these conditions, the neural networks are subjected to the consequences of a damaged blood–brain barrier (*16*), decreased regional cerebral blood flow (*17, 18*), and reduced systemic blood pressure (*18, 19*). These influences can cause secondary changes in neuronal function. Changes in the electrophysiological properties of the subsequently isolated brain tissue would demonstrate functional neuronal damage resulting from the complex physiological consequences of radiation exposure.

METHODS

Male Hartley guinea pigs (Harlan–Sprague–Dawley, Inc., Indianapolis, IN) were quarantined upon arrival and screened for evidence of disease. They were maintained in a facility accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC) and were provided commercial guinea pig chow and water *ad libitum*. Animal holding rooms were climate-controlled and circadian rhythm-adjusted. Guinea pigs weighed 150–300 g at the time of use.

Guinea pigs were irradiated (whole-body exposure) one at a time in the bilateral γ-radiation field of the AFRRI ^{60}Co facility. During radiation

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exposure (≤5 min), each animal was confined within a slotted acrylic tube to restrict its movement. The midline tissue dose to animals was either 5 Gy (delivered at 1 or 20 Gy/min) or 10 Gy (delivered at 20 Gy/min). Prior to exposure of the animals, the desired dose rates were established in an acrylic guinea pig phantom using a tissue-equivalent ionization chamber (calibration traceable to the National Institute of Standards and Technology). Dosimetric measurements were made in accordance with the American Association of Physicists in Medicine (AAPM) protocol for the determination of absorbed dose from high-energy photon and electron beams (*20*). A fraction of the total dose to the animals was contributed at a variable dose rate associated with the rise and fall of the ^{60}Co source. At a dose rate of 20 Gy/min, this fraction was about 1 Gy; at 1 Gy/min it was approximately 0.15 Gy.

Experiments were performed on brain slices isolated from the animals 30 min, 1 day, 3 days, or 5 days after exposure to γ radiation. An animal's experimental group was determined prior to radiation exposure. To control for the possible stress of the radiation procedure, sham-irradiated animals were treated similarly but not exposed to radiation. Sham exposures lasted either 5 min or 30 s for comparison with the low and high dose rates, respectively. The sham-irradiated animals were affected minimally by the procedures. Only in animals tested 30 min after a 30-s sham exposure was any change noted (i.e., an enhancement of spike generation).

Guinea pigs were anesthetized by isoflurane inhalation and euthanized by cervical dislocation. The brain was removed and the hippocampus dissected out and cut into 400- to 450-μm-thick slices with a McIlwain tissue chopper (Brinkman Instruments, Westbury, NY). Care was taken to ensure uniformity of the tissue from animal to animal. Hippocampal slices were allowed to stabilize for a minimum of 1–1½ h in artificial cerebrospinal fluid (ACSF) equilibrated with 95% O_2/5% CO_2. Composition of the ACSF is as follows: 124 m*M* NaCl, 3 m*M* KCl, 2.4 m*M* $CaCl_2$, 1.24 m*M* KH_2PO_4, 1.24 m*M* $MgSO_4$, 10 m*M* glucose, and 26 m*M* $NaHCO_3$.

After the stabilization period, a single slice was transferred to the recording chamber (Zbicz design, 21) where it was perfused continuously (1–2 ml/min) with oxygenated ACSF at 30 ± 1°C. A concentric bipolar stimulating electrode was placed in the *stratum radiatum* in field CA1 of the hippocampal slice to evoke orthodromic responses. (A schematic of the electrophysiological system is shown in Fig. 1.) Glass microelectrodes filled with 2 *N* NaCl were placed in the *stratum radiatum* of field CA1 to record the afferent volley and the population postsynaptic potential (PSP) (dendritic electrode) and in *stratum pyramidale* of field CA1 to record the population spike (somatic electrode) (Fig. 1). To reduce the variability among slices, the electrodes were always positioned in approximately the same location and recorded potentials were optimized in each slice prior to collection of data. The electrical signals from the recording electrodes were monitored on the oscilloscope and digitized and stored in a PDP11–23 minicomputer.

After placement of the electrodes, the tissue was stimulated with 300-μs current pulses once every 5 s at an intensity that produced approximately a half-maximal response. The responses were allowed to stabilize for 15–20 min before the input–output data were generated. Varying the stimulus intensity from 0 to 1 mA elicited graded orthodromic responses. The amplitude of the afferent volley, which reflects the number of presynaptic fibers firing, was proportionate to the intensity of stimulation. Three input–output curves were plotted and analyzed as described previously (*12*): (1) the relationship between the amplitude of the afferent volley and the slope of the population PSP, which indicates the ability of the tissue to transmit synaptic signals, i.e., synaptic efficacy; (2) the relationship between the slope of the population PSP and the amplitude of the population spike, which shows the ability of the synaptic signal to elicit an action potential, i.e., spike generation; and (3) the relationship between the afferent volley and the population spike, which shows the net input–output of the tissue as reflected in the amplitude of the population spike at a given stimulus intensity.

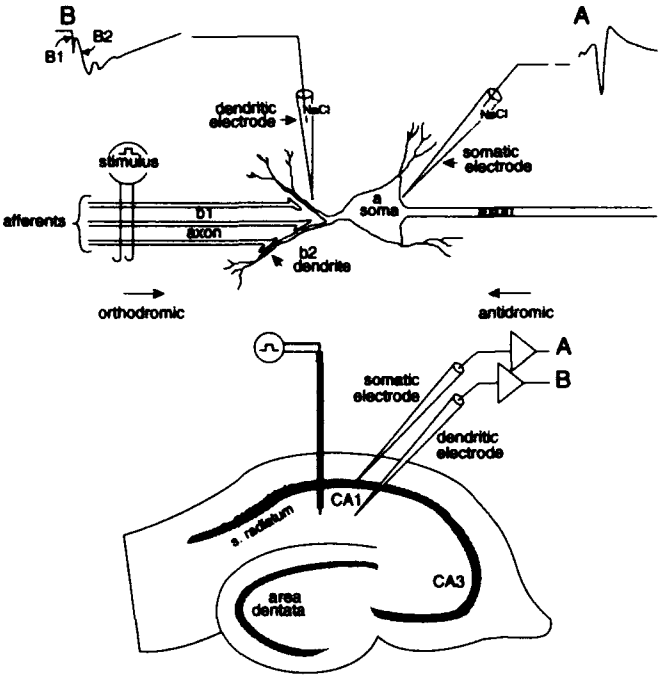

FIG. 1. Schematic of the electrophysiological system. The top diagram illustrates the components of the neural network under study. The afferent axons (b1) are stimulated. Their activity is recorded by the dendritic electrode as an afferent volley (B1). The afferent fibers synapse on dendrites (b2), which respond with a synaptic potential. The potential recorded by the dendritic electrode is the population PSP (B2). A synaptic potential is conducted to the neuronal soma (a). If it is sufficiently large, it elicits a spike. The somatic electrode records this spike as the population spike (A). The bottom diagram illustrates the location of these electrodes in the hippocampal brain slice preparation. The somatic electrode is positioned in the *s. pyramidale* of field CA1, the anatomical structure containing the neuronal somata. The stimulating electrode and the dendritic electrode are positioned in *s. radiatum* of field CA1, which contains the afferent axons and the dendrites.

Data from all slices in an experimental group were averaged and standard errors computed. A minimum of six animals (one slice each) was used in each experimental group. Data for each radiation exposure and time after irradiation were plotted, fitted by computer with the equation for a sigmoid curve, and compared to the appropriate sham-irradiated controls. Differences between the irradiated and sham-irradiated tissue were evaluated by comparing the residual sum of squares for the curves fitted to the points for each condition with the residual sum of squares for the curve fitted to all of the data together (*12*). Significance was accepted at $P < 0.05$. To evaluate quantitative changes in the input–output curves, we calculated the ratio of two parameters of the best-fitting sigmoid curves defining the input–output relationship. These parameters are the maximal response output (a) and the input required to elicit a half-maximal response (c). A decrease in the input–output curve is indicated by a decrease in the a/c ratio. These ratios and their associated standard errors were used to calculate the percentage change in the irradiated tissue compared to the sham-irradiated controls (*12*). A t test was used to evaluate significance. Under most conditions, there was agreement in the statistical significance indicated by both the change in ratio (t test) and the difference in the curves (residual sum of squares), as seen in previous studies (*12*). However, on occasion, the results of the two tests differed. Therefore, to be conservative, we accepted significance only if both of the statistical methods showed significance at $P < 0.05$.

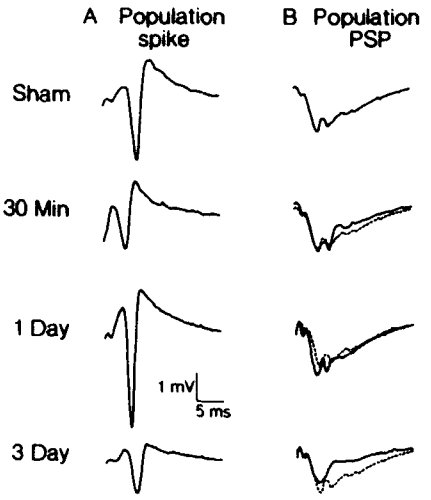

FIG. 2. Sample traces from sham-irradiated and irradiated tissue. (A) Population spikes recorded in field CA1 of *s. pyramidale*. (B) Population PSPs recorded in field CA1 of *s. radiatum*. Slices were obtained from a sham-irradiated animal (euthanized at 1 day after sham exposure) and from irradiated animals exposed to 10 Gy at 20 Gy/min euthanized at 30 min, 1 day, and 3 days after irradiation. The population PSP from the sham-irradiated tissue is superimposed (dotted line) on the response from the irradiated tissue to facilitate comparisons. All traces were elicited at the same stimulus intensity in slices from different animals. Calibration: 1 mV, 5 ms.

RESULTS

The population spike and the population PSP recorded in *s. pyramidale* and *s. radiatum*, respectively, were both sensitive to γ radiation. The changes elicited were dependent on the time after irradiation and the dose and dose rate of the exposure. Figure 2 illustrates representative responses from single slices isolated from sham-irradiated and irradiated animals. Hippocampal slices removed from animals 30 min after exposure to 10 Gy γ radiation at 20 Gy/min showed a decrease in the population spike when compared to sham-irradiated controls. The population PSP, however, was unchanged. At 1 day, the population spike amplitude had recovered beyond control levels and the synaptic potential was enhanced. At 3 and 5 days after irradiation, the population spike again was significantly reduced as was the population PSP.

Figure 3 illustrates the input–output curves obtained at 5 days after exposure to 10 Gy delivered at 20 Gy/min. For a given afferent volley amplitude, the resulting population PSP was generally smaller (Fig. 3B). Activation of more presynaptic fibers was required to produce the same size synaptic potential. In other words, the efficacy of synaptic transmission was reduced. The relationship between the size of the synaptic potential and the amplitude of the population spike (Fig. 3C) was also altered. Figure 3C shows that a given size population PSP was less capable of evoking a population spike. In other words, the mechanisms underlying spike generation were impaired. Because both synaptic efficacy and spike generation were reduced, the afferent volley elicited a smaller population spike (Fig. 3A). The net output of the neural network (the population spike) was smaller.

From this analysis, the relative contributions of changes in synaptic efficacy (Fig. 4B) and spike generation (Fig. 4C) to the net change in the population spike (Fig. 4A) can be evaluated. For example, slices obtained from animals euthanized 30 min after exposure to 10 Gy at 20 Gy/min showed no change in the population PSP. A decrease in spike generation was responsible for the decreased population spike. At 1 day after irradiation, synaptic efficacy was enhanced but spike generation had returned to control lev-

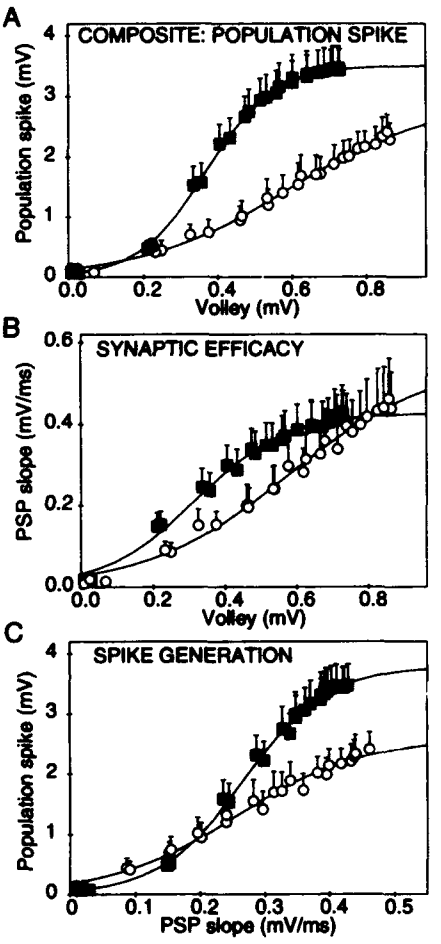

FIG. 3. Input–output curves from hippocampal slices isolated 5 days after sham irradiation (■) or 10 Gy exposure at 20 Gy/min (○). Panel A: Plot of afferent volley amplitude vs population spike amplitude reflects the net output of the neuronal population (population spike) for afferent input (afferent volley). Panel B: Plot of afferent volley vs slope of the population PSP reflects the ability of the input to elicit a synaptic potential. Panel C: Plot of slope of the population PSP vs amplitude of the population spike reflects the ability of the neurons to evoke an orthodromic action potential.

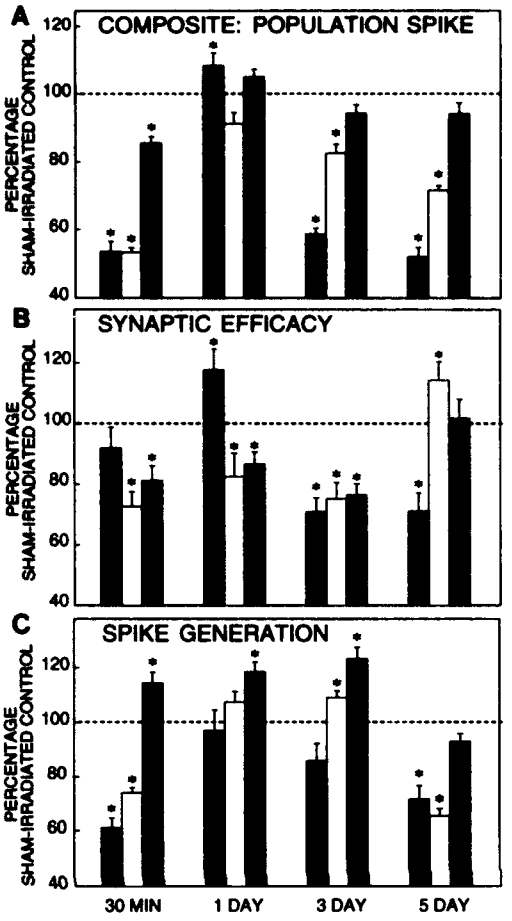

FIG. 4. Summary of the effects of whole-body γ radiation on the electrophysiological properties of the isolated hippocampus 30 min, 1 day, 3 days, and 5 days after irradiation. All radiation effects were compared to the appropriate sham-irradiated controls (100%). Significant differences are indicated with *: $P < 0.05$. For 10 Gy at 20 Gy/min (■), $n = 10$ at 30 min, $n = 9$ at 1 day, 3 days, and 5 days. For 5 Gy at 20 Gy/min (□), $n = 10$ at 30 min, $n = 8$ at 1 day, $n = 10$ at 3 days, $n = 15$ at 5 days. For 5 Gy at 1 Gy/min (■), $n = 6$ at 30 min, $n = 8$ at 1 day, $n = 6$ at 3 days, $n = 9$ at 5 days. For the high-dose-rate sham irradiation, $n = 9$ at 30 min, $n = 10$ at 1 day, 3 days, and 5 days. For the low-dose-rate sham irradiation, $n = 8$ at 30 min and 1 day, $n = 7$ at 3 days and 5 days. Panel A: Effects on the composite input–output of field CA1 of the hippocampus, based on changes in the relationship between afferent volley and population spike. Panel B: Effects on synaptic efficacy based on the relationship between afferent volley and population PSP. Panel C: Effects on spike generation based on the relationship between the population PSP and the population spike.

els, resulting in an enhanced population spike. Three days after irradiation, synaptic efficacy was reduced, yet the ability to generate spikes was unchanged. Consequently, the population spike was decreased. At 5 days, both synaptic efficacy and spike generation were reduced, resulting in a decreased population spike.

A dose of 5 Gy at the same dose rate produced a similar, but not identical, pattern of change in the electrophysiological parameters. There was an early decrease in the population spike that recovered at 1 day and subsequently declined again (Fig. 4A). Unlike the higher dose, the population spike at 1 day was not enhanced beyond the levels for sham-irradiated controls. The population PSP also failed to show the early potentiation with exposure to 5 Gy at 20 Gy/min but rather showed a significant decrease until 5 days when the population PSPs recovered beyond control levels (Fig. 4B). As with the higher dose, spike generation was reduced 30 min after irradiation, recovered to control at 1 day, and decreased again at 5 days. At 3 days after exposure to 5 Gy at 20 Gy/min, spike generation was slightly enhanced beyond that seen in the sham-irradiated controls (Fig. 4C).

Exposure of guinea pigs to 5 Gy at a lower dose rate, 1 Gy/min, also significantly affected electrophysiological properties of the hippocampal tissue (Fig. 4). As with 5 Gy at 20 Gy/min, the population PSPs were reduced in slices obtained from animals 30 min, 1 day, and 3 days after irradiation but returned to normal levels in slices isolated 5 days after irradiation (Fig. 4B). Spike generation was not reduced at the earliest time as had been seen with the higher dose rate, but was actually enhanced up to 5 days, when it returned to normal (Fig. 4C). Because of the balance between the decrease in synaptic efficacy and the enhancement in spike generation, the composite population spike was altered minimally by these radiation parameters. Only at 30 min was the population spike amplitude reduced by 5 Gy at 1 Gy/min (Fig. 4A).

A comparison of the effects of 5 Gy at the two dose rates is shown in Fig. 5. The difference in dose-rate effectiveness

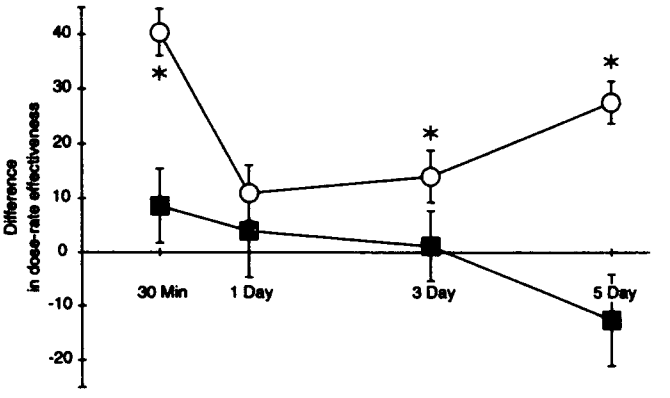

FIG. 5. Dose-rate effects of 5 Gy whole-body γ radiation on synaptic efficacy (■) and spike generation (○). Difference in dose-rate effectiveness was calculated by subtracting the effect produced by exposure at 20 Gy/min (percentage of sham-irradiated control) from the effect produced by exposure at 1 Gy/min (percentage of sham-irradiated control) at each time. This value gives an indication of the disparity between the changes produced by the two dose rates. For example, the effect of exposure at 20 Gy/min for spike generation at 5 days is approximately 60% of sham. The effect of exposure at 1 Gy/min is approximately 90%. The difference is 90% − 60% = 30%, which reflects a greater effect of the higher dose rate. The * indicates significant differences; $P < 0.05$.

was calculated by subtracting the percentage change from the sham-irradiated control produced by the higher dose rate from that produced by the lower dose rate. The larger the number, the greater the disparity in the effectiveness of the two dose rates. The dose-rate effect was striking for spike generation, especially at 30 min and 5 days. The large positive values indicated that the higher dose rate was more effective than the lower dose rate in decreasing spike generation. At 1 and 3 days, the lower dose rate enhanced spike generation more effectively than the higher dose rate. In contrast, the difference in the effects on synaptic efficacy of the two dose rates was not significant.

DISCUSSION

We have shown that γ radiation at relatively low doses can alter neuronal function significantly. The effects observed are dependent on dose, dose rate, and time after irradiation. Both the ability of the tissue to transmit synaptic potentials and the ability of those synaptic potentials to generate spikes are altered by radiation exposure. The changes in neuronal function that we observe are acute, occurring within minutes and days, in agreement with other investigators who have reported acute electrophysiological effects *in vivo*. In electroencephalographic recordings, spike activity in cat and rabbit hippocampus was observed within 30 min of exposure to 4 Gy X radiation, with changes persisting up to 7 days (*9*). Sato and Austin (*8*) reported acute increases in excitatory postsynaptic potentials in cat spinal motoneurons with 5–50 Gy X radiation. More recently, Bassant and Court (*7*) described acute changes in the firing patterns of hippocampal neurons with 4 Gy γ radiation in rabbits.

Gamma and X radiation can alter the electrophysiology of hippocampal tissue *in vitro*. Moderate doses (25–75 Gy) (*11, 12*) produce acute electrophysiological changes similar to those seen with much lower doses in the present study. Spike generation was most sensitive to dose rate with *in vivo* exposures as opposed to synaptic efficacy with *in vitro* exposures, suggesting that different molecular mechanisms are responsible for the changes under the two conditions. *In vitro*, the tissue is in a well-controlled environment, where temperature, oxygenation, and nutrients are maintained at normal levels. Studies of isolated tissue reflect the effects of radiation directly on the neurons and their immediate environment. In contrast, *in vivo*, the neuronal responses are likely to be influenced by the effects of radiation on non-neuronal elements, thereby producing physiological changes at lower radiation doses. Since we observed that the consequences of radiation are still in evidence when the tissue is removed from the animal, persistent secondary effects on the electrophysiological properties of neurons are indicated. A contribution of local and systemic factors to the effects we observed on neuronal activity may underlie the complexity of the dependencies on dose, dose rate, and time which we found.

Among the non-neuronal effects produced by ionizing radiation are acute vasogenic edema (*22, 23*), pinocytosis, and astrocytic swelling (*24*). These changes may reflect a compromised blood–brain barrier (*16*). With impaired integrity of the blood–brain barrier, neuromodulators and toxins released into the blood may gain access to the brain (*25*). Among these neuroactive substances are corticosteroids (*26*) and eicosinoids (*25*), which could cause long-lasting modulation of neuronal function (*27–30*). Systemic blood pressure decreases within minutes of exposure to at least 3 Gy γ radiation (*19*). Concurrent with changes in blood pressure is a decrease in cerebral blood flow (*17, 18*), which could produce an ischemic insult sufficient to cause degeneration of hippocampal neurons in the CA1 field (*31, 32*).

The radiation doses used in the current study are known to elicit the hemopoietic and the gastrointestinal syndromes. The observed changes in neuronal function could result from physiological consequences relating to these syndromes. Support for the possible involvement of stem cell destruction comes from the observation that protection of the bone marrow from ionizing radiation can mitigate a decrement in performance (*33*). In species that vomit, a severe emetic response occurs acutely in the dose range used in this study (*1, 10*). Accompanying the gastrointestinal syndrome are increases in plasma β-endorphins (*30*), histamine (*18, 25*), and prostaglandins (*25, 34*). In addition to released circulating factors, electrolyte transport in the ileum is altered over the course of several days after 7.5–12 Gy γ radiation in rabbits (*35, 36*). The loss of normal gastrointestinal absorption and secretion could ultimately affect the neuronal environment and modulate neuronal function.

Our results demonstrate that dose rate has a very strong influence on the changes observed after radiation exposure. At the cellular and membrane levels, several studies suggest that dose rates greater than 1 Gy/min have minimal additional effect (*37, 38*). White matter necrosis responsible for late spinal cord damage seems to show a similar limit for dose-rate sensitivity (*39, 40*). On the other hand, behavioral and electrophysiological studies have demonstrated dose-rate dependencies at higher levels. George *et al.*[1] observed that the ED_{50} for performance decrement in miniature pigs has a very steep dose-rate dependence between 5 and 20 Gy/min. Similarly, Bruner (*41*) reported a significant difference between a dose rate of 1 and 2 Gy/min on performance in monkeys. Previous electrophysiological studies in

[1] R. E. George, R. L. Chaput, and E. L. Barron, The dependence of miniature pig performance decrement upon gamma ray dose rate. Report SR72-20, Armed Forces Radiobiology Research Institute, Bethesda, MD, 1972.

the isolated hippocampal slice preparation (*12*) demonstrated more severe synaptic depression with a dose rate of 20 Gy/min compared to 5 Gy/min. As discussed above, altered performance and neuronal function are likely to be a consequence of damage to multiple systems with different sensitivities and a variety of repair and compensatory mechanisms, at both the cellular and the organ system levels. The different sensitivities to dose rate are likely to reflect, in part, the complexity of the underlying mechanisms.

The nervous system classically has been considered resistant to radiation injury, with damage seen only at very high doses (>100 Gy) or with long latencies (*13–15*). Most of the early functional changes that have been reported as well as the delayed reactions of the nervous system are usually attributed to effects on non-neuronal cells, i.e., glia and vascular endothelium (see ref. *14*). The present study conclusively demonstrates that neuronal function is impaired by low doses of γ radiation. Diverse and complex physiological influences are likely to be responsible for the neuronal deficits observed.

ACKNOWLEDGMENTS

This research was supported by the Armed Forces Radiobiology Research Institute, Defense Nuclear Agency, under work unit number 00105. Research was conducted according to the principles enunciated in the *Guide for the Care and Use of Laboratory Animals* prepared by the Institute of Animal Resources, National Research Council. We thank Drs. Larry Myers and David Keyser for their comments on the manuscript.

RECEIVED: January 19, 1993; ACCEPTED May 17, 1993

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